Remarks

Claims 1, 4-11, and 13-30 were previously pending and under examination. By this response no claims are amended. Accordingly, claims 1, 4-11, and 13-30 are currently pending and under examination. No new subject matter is introduced.

Withdrawn Rejections

Applicant acknowledges that all previous rejections have been withdrawn by the examiner with the exception of those noted below as maintained rejections.

Provisional Obviousness-Type Double Patenting Rejection

Applicant acknowledges the maintained provisional rejection of claims 1, 4-11, and 13-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/817,165. The rejection is a provisional one since none of the claims in the 10/817,165 application has been found allowable. Applicant has previously indicated that it is willing to consider filing a terminal disclaimer if necessary, at the time that claims in the instant application are to deemed to be in condition for allowance.

Rejections Under 35 U.S.C. § 112, first paragraph

The examiner has maintained the rejection of claims 1, 4-11, and 13-30, under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Pages 3-10 of the Office Action repeat the rejection found in the Final Office Action dated August 10, 2005, with the exception that the rejection based on McCluskie *et al.* has been dropped (see below). Pages 10-18 of the Office Action address the examiner's reasons for maintaining the rejection for lack of enablement. Applicant respectfully traverses this rejection and address each of the issues raised in the Office Action herein.

1. Treatment of Atopic Dermatitis

The examiner has stated that none of the examples set forth specific enablement for the specific treatment of atopic dermatitis. On page 12 the examiner specifically raised the question, "Is

the specific induction of a Th1 response and the suppression of a Th2 response specifically indicative of successful treatment of atopic dermatitis?" and has used Luo *et al.* for the proposition that the induction of a Th1 response is indicative of success for numerous treatments, for example the treatment of bladder cancer.

Applicant respectfully traverses. Applicant asserts that the specific induction of a Th1 immune response and the suppression of a Th2 immune response is indeed associated with the successful treatment of atopic dermatitis, as well as other atopic conditions and certain other diseases requiring such a shift in the immune response. The instant specification discloses that CpG oligonucleotides effectively drive the immune response towards a Th1 immune response and away from a Th2 immune response. As shown in the previously submitted declaration of Dr. Joel Kline, a Th1 immune response induced by a CpG-containing oligonucleotide is specifically effective not only against allergic asthma but also against atopic dermatitis.

Applicant agrees with the examiner that induction of a Th1 immune response is indicative of successful treatments for numerous conditions, atopic as well as certain other conditions, and further asserts that one of ordinary skill in the art would associate induction of a Th1 immune response with the treatment of such conditions. In this regard, Applicant has shown that a Th1 immune response stimulated by a CpG-containing oligonucleotide is effective against asthma and atopic dermatitis, both of which are atopic diseases. Cancer, while not an atopic disease, is nonetheless believed to be a disease that can be treated by inducing or augmenting a Th1 immune response. Luo *et al.* is cited by the examiner for the proposition that the induction of a Th1 immune response is successful for the treatment of cancer. Applicant submits there is no ambiguity or inconsistency here merely because CpG oligonucleotides can be used to treat different types of conditions. The successful treatment in these seemingly disparate conditions relates to the common underlying beneficial effect of directing an immune system response toward a Th1 response. One of ordinary skill in the art, when presented such evidence, would have reason to believe that the specific induction of a Th1 immune response would be effective against atopic dermatitis, asthma and other atopic diseases, as well as other diseases such as cancer.

2. Discussion of References Cited in Support of Lack of Enablement

Applicant thanks the examiner for her acknowledgement that the McCluskie *et al.* reference is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines) and the pending independent claims include limitations that exclude plasmid vectors (e.g. upper size limit of 100 nucleotides).

The examiner has previously cited Krieg *et al.* 2000, Weiner *et al.* 2000, Satoh *et al.* 2002, Agrawal *et al.* 2000 and Dziadzio *et al.* 2004 to show that the state of the art is unpredictable with regard to the claimed method. The examiner has further stated that "It is noted that even though these references may suggest the possibility of CpG's usefulness, they still also indicate even several years after Applicants' effective filing date that the scope of the use of the claimed composition is not enabled".

Applicant previously filed reasons to rebut each of these references. The examiner has not specifically addressed such rebuttals. Accordingly, except in connection with Weiner *et al.*, Kreig *et al.*, and WO2004/016805, further discussed below, for the sake of brevity Applicant relies on the previously submitted rebuttals rather than reproduce them here.

On page 12 of the Office Action the examiner specifically pointed to Weiner *et al.* as cautioning that "despite therapeutic promise of some CpG ODNs, all CpG ODNs are not alike and more needs to be learned about the heterogenous responses that occur based on host organism, cell subset or CpG ODN sequence" and that "the clinical effects of CpG ODN have not yet been explored and further work with the immunostimulatory nucleic acids in both the laboratory and the clinic are needed before their true promise as investigational immunological and therapeutic agents is known". Applicant points out that this is simply an opinion expressed by the authors that more research should be performed to better understand and optimize these drugs. These statements are not sufficient to demonstrate lack of enablement. Further research needs to be performed on many FDA-approved drugs. Biotechnology research is continually evolving. The law does not require, for a claim to be enabled, that further research to elucidate mechanisms of action, clinical preferences, etc., need not be performed. The reference by Weiner *et al.* is a review article summarizing *in vitro* and *in vivo* work as well as the use of CpG to promote innate immunity, as an

immune adjuvant, for the treatment of infectious disease, allergy, asthma and cancer. It is unclear as to whether these broad statements are applicable to all of these indications.

Weiner *et al.* also states that CpG ODN therapy holds promise for Th2 diseases such as allergy and asthma (*see* page 458, left column, fourth paragraph). Weiner *et al.* reports that animal studies indicate that it may be possible to use CpG ODN on an individual basis to shift the Th1/Th2 balance in patients with disease, such as allergy and asthma that are associated with a strong Th2 response (*see* page 459, right column, third paragraph). As previously indicated, the data presented in Weiner does not contradict the findings reported in the instant application but rather fits well with what is disclosed in the instant application (*see* page 8 of the previous response filed January 6, 2006).

On page 12 of the Office Action the examiner also specifically notes that Krieg *et al.* mentions that CpG DNA is a more effective Th1-like adjuvant than complete Freund's, and asserts that the pending claims do not recite the administration of any antigen and that "the teaching of Krieg *et al.* seem to suggest that it would be unlikely that the claimed method would be successful with regard to treating atopic dermatitis" (*see* page 13 of the Office Action). Applicant respectfully traverses this statement for two reasons. First, Krieg *et al.* also emphasizes that CpG DNA is effective in asthma immunotherapy even when given as a stand-alone agent without an allergen (*see* page 524, left column third paragraph). The teaching of Krieg *et al*. is in line with Applicant's disclosure that CpG DNA is effective either alone or with an allergen. Second, the current pending claims do recite that an immunostimulatory oligonucleotide may be administered in conjunction with an allergen (*see* claims 4 and 21), contrary to the examiner's assertion.

The examiner has dismissed Applicant's arguments regarding the data found in PCT Publication No. WO2004/016805 because it is "evidence of enablement post filing." Applicant submitted PCT Publication No. WO2004/016805 to rebut the examiner's prior rejection for lack of enablement, which rejection was based on post-filing date references. Case law has held that the use of a later-dated publication cannot be used to supplement an insufficient disclosure but can be used as evidence of the state of the art existing on the filing date of the application. *See* Gould v. Quigg, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987) (noting with approval that a "… later dated

publication … was offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed [invention] would have been operative."). Applicant notes that the examiner used post-filing date evidence to support a rejection of lack of enablement. Using this standard employed by the examiner, Applicant referred to PCT Publication No. WO2004/016805, not to provide enablement, but rather to demonstrate that CpG oligonucleotides having different structures but maintaining the critical CpG motif resulted in an altered immune response.

The examiner also questions whether the protocols set forth in this published patent application are performed in "the same manner as the experimental protocols of the pending application". (Office Action page 13). Applicant fails to see how this is relevant when the purpose of referring to PCT Publication No. WO2004/016805 was to provide evidence that a wide variety of CpG oligonucleotides result in an altered immune response. Applicant referred to PCT Publication No. WO2004/016805, not to show identical experimental procedures, but rather to show that one of ordinary skill in the art, using the instant specification as a guide, could use any of a large variety of CpG oligonucleotides, as claimed, to alter the immune response and so make and use the invention.

Overall, the references cited by the examiner are not sufficient to support the conclusion that the state of the art is unpredictable with regard to the use of CpG oligonucleotide in treating atopic dermatitis. To the contrary, these references provide ample *in vitro* and *in vivo* data demonstrating that administration of CpG-ODNs stimulates a Th1 response in the recipient and thus can be used to treat diseases such as asthma, allergy and atopic dermatitis.

Second, the Examiner stated that the specification, disclosing the use of a particular CpG oligonucleotide (SEQ ID NO:10) to treat asthma in a murine model, did not provide sufficient enablement for the claimed method – treating atopic dermatitis by administering to a subject an immunostimulatory CpG oligonucleotide of 8-100 nucleotides.

Applicant respectfully traverses. The specification of the instant application has disclosed a class of oligonucleotides having a common motif, a CpG dinucleotide, that can produce a Th1-biased immune response. In particular, the CpG oligonucleotides can induce monocytic cells and other immune cells to produce Th1 cytokines, including IL-12, IFN-γ and GM-CSF. *See* page 7,

lines 15-17. To support this statement, the application has provided numerous data obtained both *in vivo* and *in vitro*, using an adequate number of different CpG-containing oligonucleotides (more than 40 oligonucleotides were tested). *See e.g.*, page 20, Table 1, page 21, Table 2 and page 23, Table 3.

The data in the application, including that represented in Tables 1-3, establishes that unmethylated CpG-containing oligonucleotides are capable of inducing immune responses. The data in Table 5 demonstrates that the CpG-induced immune responses have the characteristic pattern of Th1 immune responses. *See* page 27. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating that CpG oligonucleotides can consistently drive the immune system toward a Th1 response. Pursuant to the data presented in the application, a skilled artisan would have recognized that many oligonucleotides containing the unmethylated CpG motif would be capable of invoking a Th1 immune response in a subject. In other words, the instant application is not limited to enablement of a particular CpG oligonucleotide, such as SEQ ID NO:10.

Pursuant to Chiron Corp. v. Genetech, Inc., 363 F.3d 1247, 1253 (Fed. Cir. 2004), Applicant is not required to provide an example of using a CpG oligonucleotide of 8-100 oligonucleotides and any of the disclosed formulas to treat atopic dermatitis, for the artisan's knowledge of prior art and routine experimentation can often fill gaps to interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments.

Atopic dermatitis is mediated by a Th2 immune response, and a Th1 immune response is protective against dermatitis. *See* Declaration of Dr. Joel Kline. Thus a skilled person in the art would have acknowledged that redirecting a Th2 response to a Th1 response in a subject would be effective in treating atopic dermatitis. In view of the disclosure that CpG oligonucleotides are capable of invoking a Th1 response, a person skilled in the art would recognize how CpG oligonucleotides, as recited in claim 1, can be used to treat atopic dermatitis. In addition, the references cited by the examiner also have demonstrated the promising effects of CpG oligonucleotides in promoting a Th1 immune response for treating diseases requiring a Th1 immune response. The claimed invention is enabled because the disclosure of the instant application would allow one skilled in the art to make and use the claimed invention, or, at a minimum, because

knowledge of the state of the art would allow one skilled in the art to extrapolate how to make and use the claimed invention from the disclosure of the instant application.

3. Amount of Direction or Guidance in the Specification

On page 13 of the Office Action the examiner also indicated that "the amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention." Specifically, the examiner pointed out on page 14 that "the quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the claimed oligonucleotides." Further, the examiner stated that there was no working example provided in the instant application.

Applicant respectfully traverses. In Example 12 of the instant application, mice were immunized with *Schistosoma mansoni* eggs containing an antigen that stimulates a Th2 immune response as a model of asthma. The mice were also treated with CpG ODN by i.p. administration and later exposed to the antigen intranasally. The results demonstrate that eosinophils present in the lung did not increase in the presence of CpG ODN and that the administration of CpG ODN can redirect the cytokine response of the lung to production of IFN-γ, indicating a Th1 type of immune response (*see* page 23, paragraphs 191-200). Applicant refers the examiner to the Declaration of Dr. Joel Kline (submitted September 10, 2003). This declaration demonstrates that CpG oligonucleotides are effective in the treatment of atopic dermatitis in a mouse model. The experiments performed involve mice exposed to ovalbumin antigen using a patch and injected i.p. with CpG ODN. The mice were then challenged with ovalbumin by inhalation. The results demonstrate that the administration of CpG ODN significantly reduced both airway and skin eosinophilic responses. Therefore, CpG ODN administered i.p. resulted in a decrease in eosinophils in animal models of both asthma and atopic dermatitis. The methods and data are consistent with the teachings and data described in the specification.

It is unclear if the examiner is requiring a higher standard. If the examiner is requesting that the exact protocol be written out in the specification, then the examiner is requested to provide a

legal basis for such a standard. The MPEP states that the description of the experiments in the declaration should be commensurate in scope with the application, "i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art." (MPEP 2164.05). It is respectfully submitted that the description of the experiments in the declaration satisfies this very standard. Furthermore, the data in the declaration demonstrates the use of the compounds described in the specification in the treatment of atopic dermatitis. No more is required.

Applicant presented the data in the declaration, not for purposes of enabling the claimed invention, but rather to rebut the rejection of record. MPEP 2164.05 states that "Applicant may submit factual affidavits under 37 C.F.R. § 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered." (emphasis added) An Applicant is not precluded from providing a declaration after the filing date which demonstrates that the claimed invention works. The specification as filed provides adequate enablement for the claimed invention. The examiner has asserted that the invention was unpredictable at the time of filing, as evidenced by teachings found in post-filing references. Applicant has asserted that one of skill in the art would have expected the invention to work as Applicant taught in the specification at the time the patent application was filed.

The examiner has asserted that the claimed invention was "unpredictable" and supports this view with post-filing references to show that the invention would not be expected to work even after the filing of the patent application. The data presented in the Kline declaration demonstrates that the claimed methods actually do work as Applicant stated they would in the patent application. In addition, the data presented was shown to be based on the patent application and using no more than ordinary skill without undue experimentation. Further, in terms of the examiner's concerns about the need for de novo determination of accessible target sites, modes of delivery, and formulations of the claimed oligonucleotides, it should be noted that the examples provided in the specification and in the declaration of Dr. Kline suggest the examiner's concerns are misplaced. Effective protection against asthma, and likewise against atopic dermatitis, by systemic (i.p.) administration of CpG oligonucleotide is consistent with any method that brings CpG oligonucleotide into contact with cells of the immune system.

As noted above, Applicant is not required to provide each and every piece as to how to make and use the claimed invention, for the gaps can be filled by the knowledge of a skilled person in the art or routine experimentation. *See* Chiron Corp. v. Genetech, Inc., 363 F.3d 1247 (Fed. Cir. 2004). The aforementioned prior art references have consistently supported the use of CpG to invoke a Th1 response both *in vitro* and in animal models, a common mechanism of action that contributes to the therapeutic effects of CpG oligonucleotides. These references have also demonstrated the promising therapeutic effect of immunostimulatory CpG oligonucleotides in treating diseases requiring a Th1 immune response. Moreover, data presented in the specification, including the use of a CpG oligonucleotide for the treatment of allergic asthma in a murine model, also teaches how to make and use the claimed invention. In light of the references cited by the examiner and the disclosure of the instant application, one of ordinary skill in the pertinent art, using no more than routine experimentation, would have known how to administer CpG oligonucleotides to a subject to treat atopic dermatitis by stimulating a Th1 immune response. Thus the enablement requirement under 35 U.S.C. § 112 has been satisfied. *See* In re Johnson, 282 F.2d 370, 373.

Further, actual reduction to practice prior to filing is not necessary to satisfy the enablement requirement. *See* Gould v. Quigg, 822 F.2d 1074, 1078 (Fed. Cir. 1987). MPEP 2164.02 also makes it clear that lack of working example or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the ground of lack of enablement. Accordingly, lack of a working example of the claimed invention should not be a *per se* bar to patentability for lack of enablement.

4. Correlation of in vivo and in vitro data

The examiner noted on page 14 of the Office Action that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. According to the examiner, the specification does not set forth an *in vitro* or *in vivo* animal model example that constitutes a working example that correlates with a disclosed or claimed method invention.

Applicant respectfully traverses. Applicant has presented data and asserts that it correlates with the scope of the claimed invention. The examiner has not presented any objective evidence to demonstrate why it does not correlate. Applicant has described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1-favored immune response is not only described (e.g., *see* page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 – page 54, line 5) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. Further, the Weiner reference cited by the examiner, which Applicant has shown is in line with the instant application and the data presented, states that "the observed *in vivo* data fits well with the *in vitro* data" (*see* page 457, right column, third paragraph). This observation is also true of the *in vivo* and *in vitro* data presented in the application and the declaration of Dr. Kline. Applicant asserts that a correlation between the *in vivo* and *in vitro* data is presented.

Furthermore, Applicant has specifically demonstrated correlation between *in vivo* data concerning treatment of one atopic condition, asthma, as disclosed in the specification, and *in vivo* data concerning treatment of another atopic condition, atopic dermatitis, as described in the Declaration of Dr. Joel Kline. Applicant respectfully submits that such data is extremely strong evidence that the claimed methods function *in vivo*. Accordingly, Applicant further submits that the specification does indeed set forth an *in vivo* animal model example that constitutes a working example that correlates with the claimed method invention.

Additionally, the data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude…possible inoperative substances,'

In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims.

In view of the foregoing, the office action does not provide persuasive reasons that a skilled person in the art would need undue experimentation to make and use the claimed invention. Thus, withdrawal of the rejection of claims 1, 4-11 and 13-30 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Conclusion

If, after reviewing this response, the Examiner believes that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below. If this response is not considered timely and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825. No new matter has been added.

Respectfully submitted,

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Dated: November 3, 2006